REMARKS

Reconsideration of the present application is respectfully requested.

Status of the Claims

Claims 54-56, 59-92, and 95-151 have been acted upon by the Examiner. No claims have been allowed. Claims 54-56, 59-92, and 95-151 have been canceled. Claims 152-170 have been added. Accordingly, Claims 152-170 are presented for examination.

In order to simplify the claims and to advance prosecution, applicants have canceled all the pending claims, submitted 19 new claims including only two independent claims (Claims 152 and 167), and ordered the claims in a manner to present the most logical progression to the Examiner. The new claims are based upon previously pending claims. No new matter has been added. For example, independent Claim 152 is a combination of two previously pending claims, Claims 54 and 90. Similarly, independent Claim 167 is a combination of previously pending Claims 82, 83, 86 and 87. For the Examiner's convenience, the following table identifies the currently pending new claims and the claims from which they are based.

New Claim	Previous Pending Claim(s)
152	54, 90
153	114, 115
154	116, 130
155	117, 131
156	76, 79
157	74, 109, 111
158	61, 78, 81, 96, 113
159	62, 97
160	59, 95
161	60

New Claim	Previous Pending Claim(s)
162	64, 99
163	65, 100
164	67, 102
165	68, 103
166	75, 110
167	82, 83, 86, 87
168	83, 87
169	82, 86
170	84, 85, 88, 89

35 U.S.C. §103(a) Rejections

All previously pending rejected claims have been canceled. In order to advance the prosecution, applicants will discuss the prior rejections in view of the newly presented claims.

With respect to the new independent claims, Claims 152 and 167, the prior obviousness rejections rely on the combination of Goodey *et al.* (WO 97/31947) and Matsuoka-1 *et al.* (EP 0 428 758) as evidenced by Cohn *et al.* (J. Am Chem. Soc., vol. 68, pp. 459-75, 1946), Shaklai *et al.* (J. Biol. Chem., vol. 259, pp. 3812-17) and Ohmura *et al.* (EP 0 570 916 A2).

In particular, the Examiner asserts that Goodey *et al.* teaches all the limitations of Claims 59 and 90 (now new Claim 152) except that Goodey *et al.* does not teach using albumin purification using cation exchange (CE) chromatography run in the negative mode with respect to albumin. The Examiner further asserts that Matsuoka-1 *et al.* teaches CE chromatography run in the negative mode with respect to albumin using starting concentrations of about 20 g/L (as evidenced by Cohn *et al.*). Thus, the Examiner concludes that it would have been prima facie obvious to one of ordinary skill in the art to add the CE chromatography step run in a negative

mode with respect to albumin of Matsuoka-1 *et al.* to the albumin purification method of Goodey *et al.* For the motivation to combine the references, the Examiner argues as follows:

> The motivation to do so, provided by Matsuoka *et al.*, would have been that using ion exchange in negative mode with respect to albumin resulted in efficient albumin purification with reduced amount of contaminating proteins which lead to polymer formation during heat treatment (page 2, lines 27-32). The teaching of Matsuoka *et al.* regarding the anion exchange purification therefore enhances the ability of Goodey *et al*, to obtain highly purified albumin therapeutic treatments (Goodey *et al.*, page 1, lines 1-25).

(Office Action at p. 12).

"To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143. Here, there is no suggestion or motivation to combine the references nor do the references when combined teach or suggest all the claim limitations.

A. There is no motivation to combine Goodey *et al.* and Matsuoka-1 *et al.*

Goodey *et al.* and Matsuoka-1 *et al.* are incompatible as they are directed to solving different technical problems. As such, one of skill in the art familiar with one of the references would not look to other for its teachings. Some of the key differences between Matsuoka-1 *et al.* and Goodey *et al.* are shown in the following table.

	Matsuoka-1 et al.	***Goodey et al***
1.	Matsuoka-1 is directed to the development of a purification method to isolate albumin from plasma (page 2, lines 3-5).	Goodey *et al*, insofar as it is relevant to Claim 1 of the present application, is directed to the purification of albumin from a recombinant source (see the Examples, in particular, Example 1).
2.	Matsuoka-1 reports that plasma-derived albumin may be contaminated with viruses (page 2, lines 13-15).	The recombinant albumin products treated in Goodey *et al* will not be contaminated with viruses that could be present in plasma. Goodey confirms this at page 5, lines 16-21, which states that the albumin produced has "*extremely low levels of, or...essentially free of,....viruses*" (page 5, lines 16-21)
3.	Matsuoka-1 reports that, as a result of the possibility of virus contamination of plasma-derived albumin, the albumin product is "*heat-treated generally so as to inactivate viruses which might contaminate the preparation*" (page 2, lines 13-15).	Goodey *et al* reports that recombinant albumin purified by its method does "*not normally comprise a heat treatment step*" and "*does not normally require a final pasteurisation step*" (page 6, lines 23-26).
4.	Matsuoka-1 reports that albumin becomes aggregated upon heat treatment, and that polymer in albumin solutions should be minimised in albumin preparations (page 2, lines 18-22). In other words, Matsuoka-1 is directed to the problem of avoiding the formation of albumin aggregates during heat treatment.	Goodey *et al* reports that its process provides for the production of albumin that has "*extremely low levels of, or...essentially free of,....albumin aggregates and polymers*" (page 5, lines 16-20). Thus, in Goodey *et al*, the production process used does not suffer from unacceptable levels of albumin aggregation.

	Matsuoka-1 et al.	***Goodey et al***
5.	Matsuoka-1 reports that the aggregation of its plasma-derived albumin during heat treatment is suspected to be caused by "*contaminating proteins which are unstable to heat*" (page 2, lines 18-20).	The recombinant albumin used in Goodey *et al* will not contain the same contaminants as the plasma-derived albumin used in Matsuoka-1.
6.	They key to success, with Matsuoka-1, is said to be an effective reduction in the levels of haptoglobin, transferrin and α_1-acidic glycoprotein (page 3, lines 53-55), which leads to an avoidance of polymer formation during heat treatment to inactivate viruses (page 3, line 56 - page 6, line 13)	The recombinant albumin product that is purified by Goodey *et al* would not contain any of haptoglobin, transferrin and α_1-acidic glycoprotein, because these contaminants are specific to the plasma origin of the albumin used in Matsuoka-1. A recombinant albumin purification process using, for example, a yeast system, would have contaminants such as mannosylated proteins, yeast derived pigments, and cell wall components.

As is evident from the differences described above, the Examiner's alleged motivation to combine is not valid. One of skill in the art would not be motivated to combine the negative CE step of Matsuoka-1 *et al.* from a plasma albumin purification process with the recombinant albumin purification process of Goodey *et al.* for at least the following reasons:

- The reader of Goodey *et al* knows that Goodey's method does *not* result in unacceptable levels of polymer formation. As such, there can be absolutely no reason to seek guidance from a process that is expressly intended to reduce the levels of polymer formation, as is the case with Matsuoka-1.

- The reader of Goodey *et al* knows that heat treatment is unnecessary in its process, particularly when purifying recombinant albumin. By contrast, Matsuoka-1 makes it clear that its process is intended to reduce albumin polymerization during a heating step of plasma-derived albumin. It follows, therefore, that the reader of Goodey *et al* would have absolutely no reason to use steps from Matsuoka-1 that are designed to minimize the

effect of heat treatment, when the reader of Goodey *et al* knows that heat treatment is, in any case, unnecessary.

- The reader of Goodey *et al* would know, if he consulted Matsuoka-1 (for which we can see no reason), that the method of Matsuoka-1 is said to be effective because it removes certain plasma-derived protein contaminants (specifically haptoglobin, transferrin and α_1-acidic glycoprotein). However, the reader of Goodey *et al* also knows that the plasma-derived protein contaminants mentioned in Matsuoka-1 are not present in recombinant albumin, and so there would be no reason to use methods specifically designed for the separation of albumin from these plasma-derived contaminants in a method of purifying recombinant albumin.

Thus, one of skill in the art would not be motivated to combine the CE chromatography step of Matsuoka-1 *et al.* with the albumin purification method of Goodey *et al.* The teachings of Goodey *et al* and Matsuoka-1 *et al.* are entirely incompatible. Matsuoka-1 *et al.* is expressly directed to solving a problem that one of skill in the art knows is not faced by Goodey *et al*, by removing contaminants that those skilled in the art know are not present in a recombinant albumin preparation used by Goodey *et al*, in order to minimize the detrimental effects of a heating step that is not part of the method of Gooey *et al* and which Goodey *et al* expressly teaches its reader not to be required.

Accordingly, there is no motivation or suggestion to combine the teachings of Goodey *et al.* and Matsuoka-1 *et al.* The Examiner's alleged motivation that it would have been obvious to use the negative CE step of Matsuoka-1 *et al.* with Goodey *et al.* because it "resulted in efficient albumin purification with reduced amount of contaminating proteins which lead to polymer formation during heat treatment" does not make any sense. As Goodey *et al.* and the claimed process is directed at purifying a recombinant source of albumin, the process does not involve heat treatment or the plasma-derived contaminants, and thus, there is no motivation to combine the references. Applicants respectfully request that this rejection be withdrawn.

B. The combination of Goodey *et al.* and Matsuoka-1 *et al.* does not teach or suggest all of the claim limitations of the pending claims

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). M.P.E.P. § 2143.03.

Claim 152 and its dependent claims include the following limitations:

- "placing the second albumin-containing ion exchange product, without further purification, into a final container for therapeutic use"; and
- "the albumin solution subjected to the cation exchange chromatography step that is run in the negative mode with respect to albumin has an albumin concentration of 10-250g.L^{-1}".

Likewise, Claim 167 and its dependent claims include the feature that the "the albumin solution subjected to the cation exchange chromatography step that is run in the negative mode with respect to albumin has an albumin concentration of 10-250g.L."

Even if it is obvious for the person skilled in the art to add the CE chromatography step run in a negative mode with respect to albumin in Matsuoka-1 *et al.* to the albumin purification method of Goodey *et al.* – and it is not – the combination does not disclose "placing the second albumin-containing ion exchange product, without further purification, into a final container for therapeutic use."

The claimed invention came about as a result of applicants' further development of the albumin purification processes. The purification processes defined by the claims relate to end-stage "polishing" processes that can be applied to albumin that has already been partially purified in order to obtain even more highly purified albumin.

Here, there is nothing to suggest that the addition of Matsuoka-1 *et al.*'s negative mode CE and AE steps would be added to Goodey *et al.*'s method such that no further purification steps would take place in between the second of Matsuoka-1 *et al.*'s ion exchange steps and the filling of a therapeutic container. Thus it is not obvious to combine Goodey *et al* and Matsuoka-1 *et al.* in such a way as to arrive at a method that has all of the limitations of Claim 152.

Moreover, even if it is obvious for the person skilled in the art to add the CE and AE chromatography steps run in a negative mode with respect to albumin in Matsuoka-1 *et al.* to the albumin purification method of Goodey *et al* in such a way as to ensure that Matsuoka-1 *et al.*'s negative mode CE and AE steps would be added to Goodey's method such that no further purification steps would take place in between the second of Matsuoka's ion exchange steps and the filling of a therapeutic container (which applicants deny), there is no reason to suppose that the addition would be obviously made in such a way as to further ensure that the albumin solution that is subjected to negative mode CE has an albumin concentration of 10-250 $g.L^{-1}$.

Matsuoka-1 *et al.* teaches a method in which it applies an albumin solution to negative mode CE wherein the concentration of albumin applied is, *at most*, 19.8 $g.L^{-1}$ (see the discussion on pages 38-39 of our previous submission of May 15, 2006). However, this teaching is solely in the context of purification of albumin from a paste of fraction V obtained by Cohn's method of cold alcoholic fractionation of plasma. Matsuoka-1 *et al.* attaches absolutely no significance to the concentration of albumin in the solution applied to the negative mode CE step. Similarly, those of skill in the art would not have any reason to believe that the albumin loading concentration of Matsuoka-1 *et al.* was a critical feature – particularly as the concentration was not even explicitly disclosed in the reference. Thus, even if Matsuka-1 *et al.*'s negative mode CE and AE steps were to be added to the method of Goodey *et al.*, the skilled person would have no reason to arrive at a method that was modified in such a way as to ensure that the albumin solution that is subjected to negative mode CE has an albumin concentration of 10-250 $g.L^{-1}$.

Accordingly, it would not be obvious to combine the teaching of Goodey *et al.* and Matuoka-1 *et al.* in such away to teach all the limitations of Claims 152 and 167.

Dependent Claims

All of the dependent claims, Claims 153-166 and 168-170 are nonobvious for the same reasons as discussed above.

Although applicants disagree with the Examiner's objections raised with respect to the previously pending claims equivalent to Claims 153-166 and 168-170, in order to simplify the issues for the Examiner, applicants have reserved such arguments.

Conclusion

In view of the foregoing amendments and remarks, applicants assert that the claims are in condition for allowance, and request respectfully issuance of a Notice of Allowance.

Applicants request an interview prior to the issuance of an action.

Respectfully submitted,

/Marc S. Segal/
Marc S. Segal, Esquire
Registration No. 40,163

Synnestvedt & Lechner LLP
2600 Aramark Tower
1101 Market Street
Philadelphia, PA 19107-2950
Telephone - (215) 923-4466
Facsimile - (215) 923-2189